Award Number: W81XWH-13-1-0095

TITLE: Integrated Eye Tracking and Neural Monitoring for Enhanced Assessment of Mild TBI

PRINCIPAL INVESTIGATOR: Mark L. Ettenhofer, PhD

CONTRACTING ORGANIZATION: The Henry M. Jackson Foundation (HJF)
Bethesda, MD 20817-1834

REPORT DATE: June 2017

TYPE OF REPORT: Final, Option Year 3

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
June 2017	Final, Option Year 3	08 MAR 2016 – 07 MAR 2017

4. TITLE AND SUBTITLE
Integrated Eye Tracking and Neural Monitoring for Enhanced Assessment of Mild TBI

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-13-1-0095

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Mark Ettenhofer, PhD

E-Mail: mark.ettenhofer@usuhs.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Henry M. Jackson Foundation (HJF)
6720A Rockledge Drive, Suite 100
Bethesda, MD 20817-1834

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Nearing the end of Year 4 POP (08 MAR 2016 – 07 MAR 2017), data collection for USU primary study is near completion (n=67). Data analysis for USU primary study continues. Despite administrative and technical delays during Year 4, MRI data collection was initiated during Year 4 (n=4) at the National Intrepid Center of Excellence (NICoE). As outlined in the recent SOW, the imaging sample size will be supplemented through MRI data collection efforts in the Clinical Optimization Phase. Quality assurance and a data processing pipeline for MRI data is underway. Additional Y4 accomplishments include presentation of preliminary Primary phase results at scientific meetings and colloquia, continued recruitment efforts to increase enrollment in Year 4, completion of initial hardware and software development for the Fusion Advanced Mobile Prototype (Fusion-AMP), and approval for a Y5 extension. At the end of Year 4, key milestones were approximately 4 quarters behind schedule due primarily to delays encountered in Year 1 study startup. One-year POP extension and revision of the SOW (approved at the time of submission of this report) bring current study progress approximately in line with the revised milestones.

15. SUBJECT TERMS
Nothing listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

Introduction

The objective of this project (the "Fusion Study") is to validate a combined EEG and eye tracking system aimed at assessing compromised cognitive function stemming from mild traumatic brain injury (mild TBI). Research suggests that the neural injuries resulting from mild TBI do not always produce observable performance deficits. However, subjective ratings suggest that the level of effort required to perform at a given level can be higher with mild TBI; associated neuroimaging data reveal a broader recruitment of cortical neurons to accomplish tasks in mild TBI relative to uninjured individuals [1-3]. The research described here combines information from two distinct physiological sensing approaches to make inferences about injury-related changes in cognitive function using measures that are sensitive to cognitive effort. The goal is develop methods for neurodiagnostic assessment tool that can be used in a broad range of contexts in which cognitive assessment is relevant. Validation of the integrated EEG and eye tracking system will include evaluation of these measures based on characterizations of injury severity, performance on conventional neurocognitive tests, and self-report measures. We will also include fMRI and DTI measurements to provide an objective basis for cross-validating the EEG and eye tracking system. Both the EEG and eye tracking data will be collected in the context of a dual-task experimental paradigm with visual target detection.

Keywords

TBI, concussion, saccadic, eye tracking, EEG, cognition

Overall Project Summary

Phase 1, the Fusion Pilot Study (n=30) was completed in Y3Q1. The Pilot phase was used to define methods for further study. Phase 2, the Fusion Primary Phase, was initiated in Y3Q1 and has enrolled n=67 participants in the USU portion of the study and n=4 participants in the NICoE portion of the primary study. NICoE enrollment has been limited by significant gaps in availability of NICoE scanning resources. The quantity and quality of eye tracking and EEG data obtained have been determined to be adequate to support a transition of efforts from Primary Phase to Phase 3, the Clinical Optimization Phase. MRI acquisition will be added to Phase 3 in order to make up for the shortfall of these data in Phase 2. Significant preparatory activity has been completed for the Clinical Optimization study, including submission of the IRB protocol and completion of initial hardware and software development for the Fusion Advanced Mobile Prototype (Fusion-AMP) eye tracking components. At the end of Year 4, key milestones were approximately 4 quarters behind schedule due primarily to delays encountered in Year 1 study startup. One-year POP extension and revision of the SOW (approved at the time of submission of this report) bring current study progress approximately in line with the revised milestones.

Progress is outlined below for to specific milestones delineated in the statement of work:

Data Collection Primary Study - USU. As of the end of Year 4 POP, 67 participants have been enrolled in the USU portion of the primary study (Controls: n = 27; Mild TBI: n = 21; Moderate-to-Severe: n = 15; Unclear TBI history n = 4). Continued expansion of the recruitment plan was a primary focus during this POP. Collaboration was initiated with the Center for Neuroscience and Regenerative Medicine (CNRM) in order to enhance recruitment. The CNRM recruitment core enrolls participants into one of two screening protocols (military or civilian) and then refers participants to the Fusion study based upon eligibility to CNRM funded and collaborative studies. Study personnel worked with members of the CNRM recruitment core to process and screen referrals eligible for this research effort. Flow-through of participants from the CNRM recruitment core was less than expected. Additionally,

team members attended meetings of various organizations, including Serving Together and the Family Plus Collaborative, to learn about local outreach events that are intended to provide service members with information and resources that promote mental, physical, and emotional well-being. As a result of attending these meetings, study personnel learned of and represented the Fusion study at the Brain Injury Awareness Resource Fair at the Walter Reed National Military Medical Center (WRNMMC) in March 2017. Along with other organizations, team members attended the Fifth Annual Youth Health and Fitness Fair in April 2016 to discuss this research effort with interested patrons. Advertisements have been posted at USUHS, gym and eating facilities at WRNMMC, University of Maryland, College Park (UMCP), and various TBI and rehabilitation clinics. Advertisements were also sent out electronically via the WRNMMC Intranet, and various email lists at NIH and UMCP. The study team conducts biweekly recruitment meetings to regularly track the success of our current recruitment efforts and brainstorm new sources of recruitment.

Data analysis for USU Primary Study. Continued data analyses are underway. Primary variables of interest include saccadic latency, saccadic duration, saccadic reaction time, manual reaction time, pupillary response, and several EEG/ERP components. At the end of Year 4, the USU primary study data set is near finalized. Study personnel are continuing to work to perform quality assurance, aggregate data, and refine the data processing pipeline to ensure data included in analyses are high quality. Planned analyses include assessing differences in behavioral (manual and saccadic) performance and psychophysiological responses (EEG/ERP and pupillometry) between-groups (Controls, Mild TBI, and Moderate-Severe TBI participants) and within-subjects on the Fusion cognitive tasks. Based on prior results from the pilot study and preliminary findings, we expect to see an overall effect of cognitive workload and trial type within-subjects (decreased performance and altered psychophysiological responses as task difficulty increases) in all groups. Additionally, we expect that TBI groups will have significantly degraded performance and psychophysiological response compared to controls, particularly for more challenging task components.

Data Collection Primary Study – NICoE. As of the end of Year 4 POP, 4 participants have been enrolled in the NICoE portion of the primary study (Controls: n = 3 ; Mild TBI: n = 1). As specified in the protocol, volunteers for the imaging portion of the Fusion study are recruited from the pool of DEERS eligible, USU primary study enrollees. Those who agree to volunteer, and meet NICoE's patient eligibility criteria, are contacted at a later date for NICoE data collection, including fMRI, DTI, and structural MRI.

Data Analysis for Primary Study – NICoE. Efforts are underway to perform quality assurance for MRI data collected at NICoE and to further develop the data processing pipeline so that data may be analyzed once a sufficient sample size has been obtained. Notably, the recent SOW revision adds collection of MRI data during the Clinical Optimization Phase at NMCSD. Considering that the sample size at NICoE has fallen short of expectations thus far, the addition of MRI in the Clinical Optimization Phase will provide complementary value for cross-validation of Fusion results with MRI.

Disseminate project plans and progress.

Presentations were completed at the Annual Meeting of the Society for Psychophysiological Research demonstrating pupillometric assessment of attention, cognitive load, and TBI using Fusion methodology. Additionally, Fusion methods and results were presented at a series of colloquia regarding effects of TBI and cognitive load on saccadic responses. Please see *Publications, Abstracts, and Presentations* below for information about progress in disseminating project methods, plans and progress.

Key Research Accomplishments for this Year

- Continued to enhance participant recruitment pipeline for USU primary study.
- Initiated data collection for NICoE component of the primary study.
- Development and submission of the IRB protocol for the Clinical Optimization study.
- Completion of initial hardware and software development for the Fusion Advanced Mobile Prototype (Fusion-AMP) eye tracking components.
- Obtained POP extension to continue study into Year 5.

Conclusions

The primary goal of the Fusion project is to develop and validate methods for evaluating changes in behavioral performance, saccadic performance, pupil response, and brain activation that occur at different levels of cognitive load. It is expected that individuals with TBI will demonstrate more significant performance trade-offs and greater increases in brain activation with increasing load. Preliminary analyses suggest that the Fusion tasks used for integrated eye tracking and neural monitoring are able to successfully discriminate cognitive workload across difficulty levels, and that individuals with TBI demonstrate signs of cognitive strain at levels of high load. This provides a promising basis for the extraction of valuable data relevant to detecting changes in cognitive efficacy after TBI. The final phase of the study will evaluate the Fusion Advanced Mobile Prototype (Fusion-AMP) within an Active Duty TBI clinic setting, and examine potential neural mechanism of any effects observed.

Publications, Abstracts, and Presentations Completed within Study Year 4

Manuscripts: None to report for this study period.

The following scientific presentations disseminated scientific methods and results from the USU primary study of this research effort:

1. Hershaw, J., Cordero, E., Barry, D., Kegel, J., and **Ettenhofer, M.** (2017, February). Predicting Invalid Responses Using Pupil Diameter During a Cued Attention Task. Poster presented at the 45th Annual Meeting of the International Neuropsychological Society, New Orleans, LA

2. Kegel, J., Hershaw, J., Virk, S., Safford, A., Cordero, E., & **Ettenhofer, M.L.** (2016, September). *Pupillary indices of alterations in cognitive resource allocation in TBI using a dual task paradigm.* Poster presented at the meeting of the Society for Psychophysiological Research, Minneapolis, MN.

The following invited colloquia have included dissemination of scientific methods and results of this study:

1. Ettenhofer, M.L. (March, 2017). “Emerging Technologies for Assessment and Rehabilitation of TBI.” 4th Annual TBI Symposium, Naval Medical Center San Diego, San Diego, CA.

2. Ettenhofer, M.L. (October, 2016). “The Eyes Have It: Development and Validation of Neurocognitive Eye Tracking.” Markou Seminar Series, Dept of Psychiatry, University of California, San Diego.

3. Ettenhofer, M.L. (March 2016), “Advanced Technology for Assessment and Rehabilitation of TBI.” 3rd Annual TBI Symposium of Naval Medical Center San Diego, San Diego, CA.

Inventions, Patents, and Licenses

None to report.

Reportable Outcomes

Nothing to report.

Other Achievements

Nothing to report.

References

1. McAllister, T.W., et al., *Differential working memory load effects after mild traumatic brain injury.* Neuroimage, 2001. **14**(5): p. 1004-12.
2. Chen, J.K., et al., *Functional abnormalities in symptomatic concussed athletes: an fMRI study.* Neuroimage, 2004. **22**(1): p. 68-82.
3. McAllister, T., et al., *Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study.* Neurology, 1999. **53**(6): p. 1300-8.

Appendices

There are no appendices for this report.

Supporting Data

None.

Integrated Eye Tracking and Neural Monitoring for Enhanced Assessment of Mild TBI

Psychological Health, Polytrauma, and Operational Health (PHPOH), Award W81XWH-13-1-0095

PI: Mark L. Ettenhofer, Ph.D. **Org:** Henry Jackson Foundation (HJF) / Uniformed Services University (USU)

Award Amount: $3,311,604

DMRDP

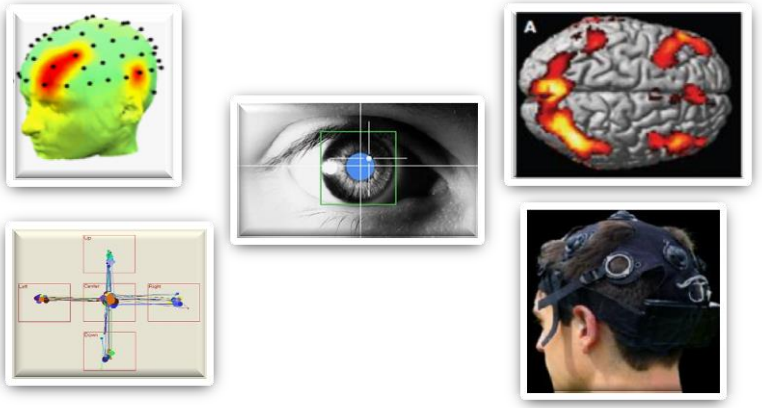
Study Aims

This project will develop and validate an integrated eye tracking/EEG system to assess cognitive efficacy after TBI.

- **Aim 1:** Develop and validate algorithms to measure cognitive efficacy after TBI using combined EEG and eye tracking.
- **Aim 2:** Identify mechanisms for reduced cognitive efficacy after mild TBI and cross-validate EEG-based results with eye-tracking enabled fMRI and DTI.
- **Aim 3:** Optimize a clinically-feasible integrated EEG/eye tracking assessment system for future commercialization.

Approach

- Fusion Tests will be developed and validated within PC-, VR-, and MRI-based environments using separate groups of healthy controls and mild and moderate TBI.



The Phase 1 pilot study is completed with 30 participant enrolled. Phase 2 at USU is functionally complete, with 67 participants enrolled and analysis underway. Development of the Fusion Advanced Mobile Prototype (Fusion-AMP) is complete for eye tracking components. The IRB protocol for Phase 3 Clinical Optimization has been submitted. MRI cross-validation will be added to Phase 3.

Timeline and Cost

Activities	Year 1	Year 2	Year 3	Year 4
IRB, Startup, and Pilot Testing				
Collect eye tracking / EEG data (Aim 1)				
Collect eye tracking / MRI data (Aim 2)				
Optimize sensors and algorithms for clinical use (Aim 3)				
Data Analysis & Dissemination				
Estimated Total Budget ($K)	771	782	810	950

Goals & Milestones

- ✓ Project startup and IRB approval
- ✓ Complete Phase 1 development and pilot study
- ✓ Revise methods for Phase 2
- ✓ Complete Phase 2 eye-tracking/EEG data collection
- ▪ Complete Phase 2/3 MRI data collection
- ▪ Complete Phase 2 analysis
- ✓ Submit IRB protocol for clinical optimization study
- ▪ Complete Phase 3 eye-tracking/EEG data collection
- ▪ Complete Phase 3 analysis and dissemination

Comments/Challenges/Issues/Concerns

Efforts are currently focused on initiating the phase 3 optimization study, to be completed during Year 5. Additional MRI cross-validation of eye tracking / EEG measurements will be added to Phase 3. Additional staff are being recruited to support these efforts at NMCSD.

Budget Expenditure to Date

Projected Expenditure (Year 4): $1,152,397.45

Actual Expenditure (Y4Q4): $136,360.14

Actual Expenditure to date (not including open expenses): $2,199,436.29